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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,410	08/04/2003	Stevan P. Tofovic	007278-10	6070

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EXAMINER	
CLAYTOR, DEIRDRE RENEE	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
05/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,410	TOFOVIC ET AL.	
	Examiner	Art Unit	
	Renee Claytor	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Reconsideration

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/2/2008 has been entered.

Response to Arguments

Applicants have amended claims 1-21 to remove the "prevention" language to overcome the 35 USC 112, first paragraph rejection. Accordingly, the rejection is hereby withdrawn.

Applicant's arguments over the 35 USC 103 rejections have been considered. Applicants assert throughout the response that they do not feel like all arguments have been addressed by the Examiner to date. It is noted that the Examiner has read all the references and specification in detail and has addressed the claims, as written, and all arguments accordingly in both the previous Final Action dated 10/2/2007 and the Advisory Action dated 12/26/2007. Regarding the Tofovic et al. reference, Applicants argue that it is merely shown that 2-OHE "attenuates the development of renal disease in genetic nephropathy associated with obesity and the metabolic syndrome" and do not feel that it is clear how attenuation of a genetic disease somehow makes obvious claims

to treating drug induced kidney disease. Applicants further assert that Tofovic et al. do not suggest modifying its teachings to treat drug-induced conditions. Applicant's further attempt to correlate the USC 112, first paragraph rejection with the present rejection by stating that the 35 USC 112 rejection states that this case involves "an unpredictable and undeveloped art" and that by this statement there would no reasonable expectation of success in modifying Tofovic to treat the conditions of the instant application.

As discussed in previous arguments, it is again pointed out that all of the conditions listed in Tofovic et al. are associated with nephropathies. Regardless of how the kidney disease originated, it is obvious that the treatment would effectively treat a kidney disease regardless of it is drug-induced or naturally occurring. Unless Applicants can show data that contradicts this, it remains obvious to a person of ordinary skill in the art that treatment of a kidney disease would be the same regardless of its etiology. It is not clear why one would assume that because the kidney disease is drug-induced, treatment of a kidney disease that is not drug-induced would be different. The Examiner is providing a reference for discussion purposes only entitled "Assessment of Nephrotoxcity" by Prescott in which forms of nephropathy, such as proteinuria, are also drug-induced. The main differences between nephropathies and nephrotoxicity is that conventional clinical investigation of renal function is of limited value in nephrotoxicity (see entire paper). However, there is no apparent difference between the actual condition, i.e. proteinuria, regardless of its etiology. In response to the attempt to correlate the 35 USC 112 rejection with the present injection, it is noted by the Examiner

that the statement made in the 35 USC 112 rejection were addressing the claim limitation of "prevention" and not the case of treating nephrotoxicity as a whole.

Applicant's arguments regarding the Xiao reference have been fully considered. It is once again pointed out that Applicants assert that the Examiner did not even address the arguments made against this reference. It is noted that the Examiner has read all the references and specification in detail and has addressed the claims, as written, and all arguments accordingly. In particular, Applicants asserts that the Examiner has mis-characterized the teachings of the reference and assert that Xiao et al. conclude that because estradiol induces NO synthesis in GECs and 2-hydroxyestradiol does not induce NO synthesis, it would not protect against renal disease and teaches away from the present invention.

In response to the above arguments, it is noted that Xiao et al. does teach that estradiol stimulates endothelial cell-derived NO synthesis and that decreased NO synthesis is associated with the pathogenesis of renal disease. However, it is noted that this information relates to estradiol and not its metabolites. Further, Xiao et al. state that this is a hypothesis. Xiao et al. does teach that metabolites are effective at inhibiting GMC growth by inhibiting DNA synthesis, collagen synthesis, and cell proliferation (second paragraph, Figures 4 and 5) and the authors conclude that the metabolites may prevent glomerulosclerosis by the inhibition of abnormal growth of GMC's. Therefore, it is evident that the metabolites are acting via a different mechanism than estradiol but are more effective in inhibiting growth of GMC's.

Applicant's arguments over Tofovic et al. and Xiao et al. in view of Allison et al. have been considered. In particular, Applicants have concentrated on the arguments set forth for the Tofovic and Xiao references which have been addressed above.

Applicants have amended the claims to remove the "prevention" language from the claims which is sufficient to overcome the 35 USC 112, first paragraph rejection and it is hereby withdrawn.

Please see the following grounds of rejection given below for Applicant's convenience.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tofovic et al. "Renoprotective effects of 2-hydroxyestradiol", *J Am Soc Nephrol* 12: 86A, 2001.

Tofovic et al. teach that chronic treatment with 2-hydroxyestradiol (2-OHE) significantly reduced symptoms of nephropathy, such as proteinuria (meeting the limitations of claims 5-6 and 8), glomerulosclerosis (meeting the limitation of claims 9-10 and 12), and interstitial inflammation (meeting the limitation of claims 13-14 and 16) in male obese rats, which is a model of nephropathy (see entire abstract).

Regarding the conditions cited in claims 1, 2, 9, 13, 17, and 21, it is considered that these conditions are all associated with nephropathy; therefore, it is obvious that the teachings of Tofovic et al. would treat the conditions listed in the above claims.

Tofovic et al. does not teach that the conditions listed in claims 1, 2, 9, 13, 17, and 21 are drug-induced; however, these pathologies of the kidney would display the same symptoms regardless of if it is drug-induced or a natural occurrence, so the treatment with estradiol metabolites would have the same results. One having ordinary skill in the art would have been motivated to extend the teachings of Tofovic et al. to treat various forms of nephropathies with estradiol metabolites because the prior art teaches that an estradiol metabolite is effective at treating various types of nephropathies.

Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xiao, S. et al. "Effects of estradiol and its metabolites on glomerular endothelial nitric oxide synthesis and mesangial cell growth", Hypertension, 2001; 37; 645-650.

Xiao et al. teach that the growth of glomerular mesangial cells (GMC) is associated with the pathogenesis of renal diseases (Pg. 645, second paragraph). It is further taught that estradiol and its hydroxy and methoxy metabolites inhibit glomerular mesangial cell (GMC) growth by inhibiting DNA synthesis, collagen synthesis (meeting the limitations of claims 21-22 and 24), and cell proliferation (meeting the limitations of claims 17-18 and 20; pg. 647, second paragraph and Figures 4 and 5). The authors

conclude that estradiol metabolites may prevent glomerulosclerosis by this inhibition of abnormal growth of GMC's (further meeting the limitation of claims 9-10 and 12; pg. 648, first paragraph). It is further taught that the hydroxy and methoxy metabolites of estradiol are more potent than estradiol at inhibiting the growth of GMC's (pg. 647, second paragraph and Figures 4 and 5).

Regarding the conditions cited in claims 1, 2, 9, 13, 17, and 21, it is considered that these conditions are all associated with nephropathy; therefore, it is obvious that the teachings of Tofovic et al. would treat the conditions listed in the above claims.

Xiao et al. does not teach that the conditions listed in claims 1, 2, 9, 13, 17, and 21 are drug-induced; however, these pathologies of the kidney would display the same symptoms regardless of if it is drug-induced or a natural occurrence, so the treatment with estradiol metabolites would have the same results. Because the prior art teaches that estradiol metabolites are renoprotective in cells modeling renal pathogenesis, one having ordinary skill in the art would have been motivated to extend the findings of Xiao et al. to *in vivo* models of nephropathies to evaluate the renoprotective effects of these compounds.

Claims 3, 7, 11, 15, 19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tofovic et al. and Xiao et al. as applied in the above rejections and in view of Allison et al. (U.S. Pg-Pub 2006/0083778).

Tofovic et al. and Xiao et al. do not teach a controlled release formulation.

Allison et al. teach sustained release formulations of estradiol metabolites, including 2-hydroxyestradiol, 2-methoxyestradiol, 4-hydroxyestradiol and 4-methoxyestradiol (meeting the limitations of claims 3, 7, 11, 15, 19, and 23; paragraph 0007, 0008, 0010).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Tofovic et al. and Xiao et al., which teach that estradiol metabolites induce renoprotective effects with Allison which teaches sustained drug delivery of estradiol metabolites. One having ordinary skill in the art would have been motivated to formulate controlled release delivery of estradiol metabolites in an extended release drug delivery device to maintain therapeutic blood levels.

Conclusion

No claims are allowed.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is (571)272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Renee Claytor

/SREENI PADMANABHAN/
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